81601-31

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	20.04.2004
Applicant's or agent's file reference	**REPLY DUE** **within 3 month(s)** from the above date of mailing
International application No. PCT/CA 03/00850	International filing date *(day/month/year)* 05.06.2003
Priority date *(day/month/year)* 05.06.2002	
International Patent Classification (IPC) or both national classification and IPC C12N15/90, C12N15/90	
Applicant HER MAJESTY IN RIGHT OF CANADA AS REPRESENTED ...	

NKS
due: July 20/04
ON DOCKET
clerk: July 19/04

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is:

DOC PLA BK

Name and mailing address of the international preliminary examining authority:

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Authorized Officer

Formalities officer (incl. extension of time limits)
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Form PCT/IPEA/408 (Cover Sheet) (January 2004)

I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-181 as originally filed

Sequence listings part of the description, Pages

1-3 received on 11.08.2003 with letter of 08.08.2003

Claims, Numbers

1-23 as originally filed

Drawings, Sheets

1/15-15/15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 7, with regard to IA: 1-4,18-20 (all partially)

   because:

   ☒ the said international application, or the said claims Nos. with regard to IA: 1-4,18-20 (all partially) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 7

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-5,22,23 (no)
Inventive step (IS)	Claims	6-9,11-21 (no)
Industrial applicability (IA)	Claims	-

2. Citations and explanations

   see separate sheet

Re Item III

Claims 1-4 and 18-20 inter alia relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT (i.e. method of treatment of the human or animal body). Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: DATTA H J ET AL: "Intracellular generation of single-stranded DNA for chromosomal triplex formation and induced recombination." NUCLEIC ACIDS RESEARCH. ENGLAND 15 DEC 2001, vol. 29, no. 24, 15 December 2001 (2001-12-15), pages 5140-5147, XP002253387 ISSN: 1362-4962

D2: J-R MAO ET AL: "Gene regulation by antisense DNA produced in vivo" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 270, no. 34, 25 August 1995 (1995-08-25), pages 19684-19687, XP002132578 ISSN: 0021-9258

D3: MIROCHNITCHENKO O ET AL: "Production of single-stranded DNA in mammalian cells by means of a bacterial retron" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 269, no. 4, 28 January 1994 (1994-01-28), pages 2380-2383, XP002132577 ISSN: 0021-9258

1. Subject matter

Present application relates to the modification of target nucleic acids in a host genome by homologous recombination with in vivo expressed ssDNA or RNA-DNA hybrids. Said expression is achieved from bacterial retrons which have been transfected into eucaryotic cells (for example yeast). To increase the efficiency of the process a reverse transcriptase was targeted to the nucleus by means of a nuclear localization sequence (NLS).

2. Novelty (Art. 33(2) PCT)

The prior art reports homologous recombination with in vivo expressed ssDNAs (D1). Furthermore, it contains the step of reverse transcription of a gene targeting construct (D1, Fig. 1) and the reverse transcribed sequence is homologous to a target locus and comprises a modification compared to the target nucleic acid.

Claims 1-5, 22 and 23 lack novelty (Art. 33(2) PCT).

3. Inventive step (Art. 33(3) PCT)

Prior art document D1 is considered closest prior art for present application. The difference to present application lies in the use of a different in vivo expression system: reverse transcription from a MoMuLV inverted repeat sequence combined with a restriction enzyme system to release a ssDNA. The technical problem imposed by this difference can be formulated as: provision of a method of in vivo ssDNA expression for homologous recombination which does not rely on cleavage by a restriction enzyme subsequent to reverse transcription. The solution has been provided in present application with the use of bacterial retrons as expression vectors.
However, this solution cannot be considered inventive because the expression of ssDNAs by retrons in eukaryotic cells to form triple helices has been described in the prior art (D2, p. 19687, last paragraph - p. 19688, first paragraph). Moreover, the person skilled in the art was aware that triple helix forming ssDNA was the gene targeting agent which had been successfully employed in D1 (p. 5144, last paragraph-p. 5145, first paragraph). The combination of D1 and D2 to arrive at the solution of present application was thus obvious for the person skilled in the art.

Claims 6-9 and 11-21 lack inventive step (Art. 33(3) PCT).

The targeting of a reverse transcriptase to the nucleus by means of an NLS was not obvious from the prior art and can thus be considered inventive. An indication relating to the localization of RT is given in D3: "The comparatively low synthesis of msDNA in transfected mammalian cells may be due to highly organized compartmentalization of eukaryotic cells, which may lower the efficiency of RT to form a complex wih the primary transcript of the retron." (D3, p. 2382, right column, l. 27-31). However, the person skilled in the art is not provided with a hint how to overcome this problem.

Claim 10 is considered inventive (Art. 33(3) PCT).

4. Industrial application

For the assessment of the present claims 1-4, 18-20 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.